## REMARKS

Claims 61-63, 65-66, 77, 79-81, 86, 87, 91, 93-101 and 104-115 were pending. Claims 96-100 were previously withdrawn. Claim 61 has been amended. Thus, upon entry of this amendment, claims 61-63, 65-66, 77, 79-81, 86, 87, 91, 93-101 and 104-115 will be pending in the application.

No new matter has been added.

Applicants reserve the right to pursue the subject matter of the claims as originally filed in this application or in another related application. In view of the foregoing claim amendments and the arguments set forth below, Applicants respectfully submit that the claims are now in condition for allowance.

### *Acknowledgement of Examiner Interview*

Applicants gratefully acknowledge the courtesy of an in-person interview with the Examiner and her supervisor Robert Mondesi on April 27, 2010, during which the presently pending claims and outstanding rejections under 35 U.S.C. §112, first paragraph were discussed. Specifically, proposed claim amendments were discussed relating to the nature of the antigen, LTA, to which the claimed monoclonal antibodies specifically bind. Applicants discussed Fisher *et al.*[1] which illustrates that the art has established that LTA is a well characterized antigen, of uniform structure on diverse Gram positive bacteria.

Applicants also discussed data which supports the use of the claimed antibodies to prevent and treat staphylococcal infection in neonates. This data includes *in vivo* data in animal models described in Applicants' specification as well as human clinical data as described in Weisman.[2] The Examiner asked that we provide further explanation with respect to the *in vivo* data in Applicants' specification, the neonatal animal model described therein, its acceptance in the art, and our human clinical data. Each of these topics is discussed in the following subsections.

[1] Fisher et al., On the basic structure of poly(glycerolphosphate) lipoteichoic acids. *Biochem. Cell Biol.* vol. 68, 1990, previously submitted as Appendix A with Applicants' Amendment and Response of July 17, 2009.
[2] Weisman. Archives de pediatrie 14 (2007) S31-S34, previously submitted as Appendix D with Applicants' Amendment and Response of July 17, 2009.

*In Vivo* Data in the Specification

Applicants' specification teaches that "treatment or prevention of an infection by Gram positive bacteria employs lethal models of sepsis that measure clearance and protection" and that "a particularly useful animal model comprises administering an antibody and a Gram positive organism to an immunocompromised (*e.g.,* an immature) animal, followed by evaluating whether the antibody reduces mortality of the animal or enhances clearance of the organism from the animal." [3]

Applicants' specification further teaches that

> Clearance is evaluated by determining whether the pharmaceutical composition enhances clearance of the infectious agent from the animal. This is typically determined from a sample of biological fluid, such as blood, peritoneal fluid, or cerebrospinal fluid. The infectious agent is cultured from the biological fluid in a manner suitable for growth or identification of the surviving infectious agent. From samples of fluid taken over a period of time after treatment, one skilled in the art can determine the effect of the pharmaceutical composition on the ability of the animal to clear the infectious agent. Further data may be obtained by measuring over a period of time, preferably a period of days, survival of animals to which the pharmaceutical composition is administered. Typically, both sets of data are utilized. Results are considered positive in the pharmaceutical composition enhances clearance or decreases mortality.[4]

In a working example, Applicants demonstrate that treatment with a monoclonal antibody of the invention enhances survival to infections with both coagulase positive and coagulase negative staphylococci in a neonatal model of lethal infection. The experiment is described as follows:

> Two day old Wistar rats were injected with $10^6$ *S. aureus* (type 5, ATCC 12605) subcutaneously just cephalad to the tail. Approximately 30 minutes before and 24 and 48 hours after infection, 0.2 ml MAB 96-110 (320 μg) was given IP. Control animals were given an equal volume of saline or a control MAB not directed against Staphylococci. All animals were observed daily for five days to determine survival.[5]

Applicants' report that "MAB96-110 enhanced survival in this lethal neo-natal model of coagulase positive staphylococcus sepsis (FIG. 3): 8/15 survived after treatment with MAB 96-110, and 0/10 survived with Control MAB or 2/25 with saline treatment."[6]

---

[3] The specification, Example 1 at page 8, paragraph [0108].
[4] The specification, Example 1 at page 8, paragraph [0109].
[5] The specification, Example 3 at page 11, paragraph [0132].
[6] The specification, Example 3 at page 11, paragraph [0133].

In another working example, entitled "In Vivo Protective Efficacy," Applicants describe an experiment in which a monoclonal antibody of the invention enhanced survival of neonatal animals following treatment. Specifically, Example 12 of the specification describes the following.

> The effect of the chimeric MAB 96-110 was then analyzed in a neonatal staphylococcal model using suckling rats with a foreign body infection. Two day old Wistar rats were treated with lipid emulsion (as is standard in newborn care for nutritional purposes) 0.2 ml, 20% IP on day -1 and again on day +1 and +2 to induce further compromise of the immune system. In two studies, we injected approximately 5 x $10^7$ of four different strains of *S. epidermidis*, identified below in Table 11 SQ through a plastic catheter and the catheter was left in place under the skin. Saline, 0.2 ml, or MAB 96-110, 0.2 ml (dose of 50-60 mg/kg), was given IP 30 min before and 24 hours after infection. The animals were followed for 5 days.
>
> As set forth in Table 11, in study I, survival for animals receiving MAB ranged from 67% to 83%, with an average of 76%, in contrast to saline treatment, which ranged from 33% to 50%, with an average of 39%. Study II showed even more impressive results. Survival for animals treated with MAB ranged from 83% to 100%, with 90% average, compared to the saline controls at 33% to 50%, with an average of 40%.[7]

Thus, Applicants specification describes *in vivo* studies in which efficacy of the claimed monoclonal antibodies was established in a neonatal animal model. This neonatal animal model is analogous to the situation with very-low-birth-weight infants, who are at high risk for hospital-acquired sepsis. Staphylococci, including *S. epidermidis* and *S. aureus* are responsible for a majority of hospital-acquired sepsis. Significantly, Applicants data demonstrates protection against infection by these organisms in appropriate animal models.

Recognition of the Animal Model in the Art

Evidence that the animal model used by Applicants is an appropriate model of human neonates is found by other investigators who used a similar model to study the efficacy of therapies for neonatal sepsis. Like the present Applicants, Venkatesh *et al.*[8] were also studying sepsis, which is a major cause of neonatal mortality and morbidity. In addition to coagulate-negative staphylococci ("CoNs") and *S. aureus* another common causative organism of late-onset sepsis in very-low birth-weight infants is *Candida albicans*. To better understand

[7] The specification, Example 12 at page 16, paragraph [0172].

[8] Venkatesh *et al. Antimicrobial Agents and Chemotherapy* 51(4):1240-1245 (2007) submitted herewith as Appendix E.

coinfection and develop effective strategies for treatment and prevention, Venkatesh and co-workers developed a neonatal model of coinfection with CoNS and *Candida* in the neonatal suckling rat, the same animal model used by Applicants. In their discussion, Venkatesh *et al.* state "[n]eonatal animals are different from adult animals in their responses to infection, hence the need for a neonatal model."[9]

Under the subheading "Animals," Venkatesh *et al.* describe an experiment in which "[o]ne to 2-day-old pups received 0.2 ml of 20% intralipid solution intraperitoneally as two doses on the first day of the study 4 h apart and as one dose each on day 2 and day 3 of the study."[10] As explained by Venkatesh *et al.*, the purpose of the intralipid suspension was to "obtain an immunosuppressive effect, probably effected through reticuloendothelial cell system blockade."[11] Similarly, in Applicants' experiment described above (Example 12), "two day old Wistar rats were treated with lipid emulsion …to induce further compromise of the immune system." Next, Venkatesh *et al.* infected the pups "subcutaneously with 0.2 ml of $10^9$ CFU/ml (dose of 2 x $10^8$ CFU, which is the 50% lethal dose) or $10^7$ CFU/ml (dose of 2 x $10^6$ CFU, which is sublethal dose) of *S. epidermidis* or *C. albicans* or both, in different combinations on day 2 and day 3 of the study."[12] Drug (*i.e.,* the antifungal agent fluconazole) was then administered intraperitoneally at 10 mg/kg body weight/day for 4 days, beginning 24 h before infection. Animal survival was assessed.

In discussing their results, Venkatesh *et al.* conclude "[t]he neonatal rat coinfection model described here is analogous to the situation in premature infants who are at risk for multiple infections and coinfection. Our data reaffirm the beneficial effects of fluconazole prophylaxis in high-risk infants."[13] Thus, not only do Venkatesh *et al.* use the same rat neonatal animal model to study the human neonate as Applicants, but they conclude that the results in the model validate a current therapeutic regimen in humans.

Applicants Human Clinical Data

Additional evidence of the relevance of Applicants' data in the neonatal rat model is the fact that this data was a crucial step in advancing a monoclonal antibody within the scope of the

[9] Venkatesh *et al.* at page 1243, left column, first paragraph under the subheading "Discussion."
[10] Venkatesh *et al.* at page at page 1241, left column.
[11] *Id.*
[12] *Id.*
[13] Venkatesh *et al.* at page 1244, right column, last paragraph through page 1245, first paragraph.

invention into humans. As reported by Weisman *et al.* (2009), "on the basis of preclinical pagibaximab bactericidal activity against a number of clinical isolates *in vitro* and in staphylococcal sepsis models in suckling animals, we have selected 500μg/ml as the putative protective level of this antibody [for human neonates]."[14] Pagibaximab is the same anti-LTA murine/human chimeric monoclonal antibody described in Applicants' specification as "chimeric MAB 96-110" and was used in the working examples described above. Notably, Weisman *et al.* looked to the serum concentration of antibody in the suckling rat model to design their Phase I/II clinical trial.

> In a suckling rat model of sepsis caused by CONS, pagibaximab significantly increased survival at a dose of 80 mg/kg of body weight ($P$= 0.0007), and the effect of 40 mg/kg was significantly lower. This was associated with suckling rat serum pagibaximab concentrations of approximately 275 to 400 μg/ml….In view of the fact that VLBW [very-low-birth-weight] infants have compromised innate immunity, we hypothesized that we needed to have excess antibody to ensure bactericidal activity….For this reason, we selected 500 μg/ml of antibody as the level which we hypothesized would be protective.[15]

Thus, Weisman *et al.* based the dosing for this safely, tolerability and pharmacokinetics study in the human neonate on the effective levels of antibody in the neonatal rat model. At the end of this study the investigators concluded, "[t]herefore, passive immunization with pagibaximab could be a potentially important step in preventing all neonatal staphylococcal infection."[16] As discussed in the in-person interview, this Phase I/II safety study supported the filing of a Phase II-III efficacy study of this monoclonal antibody which is currently underway. Information about this trail can be found at http://www.clinicaltrials.gov/ct2/show/NCT00646399

Prevention and Treatment of Infection

In discussing the concept of "passive immunization" (*i.e.,* the transfer of active humoral immunity in the form of antibodies to a subject) during the in-person interview, the Examiner asked that we provide additional evidence in support of the use of passive immunization to treat bacterial infection. It is Applicants' understanding that during the in-person interview both the

[14] Weisman *et al.*, *Antimicrobial Agents and Chemotherapy*, 53(7):2879-2886 (2009) submitted herewith as Appendix F.
[15] Weisman *et al.* at page 2879 bottom right column through page 2880, left column, first full paragraph.
[16] Weisman *et al.* at page 2884, right column, last full paragraph under "Discussion".

Examiner and her supervisor agreed that Applicants' specification demonstrates that passive immunization of the claimed monoclonal antibodies results in protection (prevention) against infection. Accordingly, further discussion of "prevention" is provided in the context of the Examiner's section 112 rejection below.

With respect to the use of passive immunization to treat infectious disease, prior to the advent of antibiotics, antibodies were the only specific agents for the treatment of certain infections. In a review article in 2000, Keller and Stiehm conclude "[a]lthough this role has largely been supplanted by antibiotics, there still remains a crucial role for antibody in the treatment of certain infectious diseases (Table 1)."[17] Table 1 of this review is a summary of the efficacy of antibody in the prevention and treatment of infectious diseases, both bacterial and viral. Notably, with respect to bacterial infections, there are a number of "Proven" treatments using antibodies, in particular, respiratory infections (human immunoglobulin to treat *H. influenza*), diphtheria (equine diphtheria antitoxin), tetanus (human tetanus immune globulin), and *Clostridium botulinum* (equine and human botulinum immunoglobulin).[18]

With respect to staphylococcal infections, the authors report the "Probable" benefit of "IVIG" (pooled human immunoglobulin for intravenous use) in the treatment of staphylococcal toxic shock syndrome and antibiotic resistance.[19] Of relevance to the present invention, Keller and Stiehm report, "[a] second situation where antibody may be of value is in the prevention of *Staphylococcal epidermidis* infection in the newborn particularly premature infants." [20] With respect to treatment, the authors report "Fisher et al. (50) have studied IVIG in the ***treatment*** of *S. epidermidis* infections in suckling rats and have demonstrated a potential benefit."(Emphasis added.)[21] They further note that "[a] final use of IVIG in staphylococcal infection is in the ***treatment*** of antibiotic-resistant chronic staphylococcal infection in addition to antibiotics." (Emphasis added.)[22]

The authors also highlight clinical studies of IVIG in the prevention and treatment of infection in newborn infants and conclude "meta-analysis of 12 prophylaxis studies showed a

[17] Keller and Stiehm, *Clinical Microbiology Reviews,* 13(4):602-614 (2000), submitted herewith as Appendix G.
[18] Keller and Stiehm at page 603, Table 1.
[19] *Id.*
[20] Keller and Stiehm at page 604, right column, last full paragraph.
[21] *Id.*
[22] Keller and Stiehm at page 604, right column, last full paragraph through page 605, left column, first paragraph.

modest protective effect."[23] Likewise, for the ***treatment*** of neonatal sepsis, the authors report, "a meta-analysis of three controlled studies showed a ***clear beneficial effect*** (six-fold decrease in mortality)." (Emphasis added.)[24] They thus conclude, "IVIG is not indicated routinely for the prevention of neonatal infections, but it may be of some value in the infected newborn not responding to antibiotics."[25]

In the final section of this review where the authors "LOOK TO THE FUTURE" they conclude "[t]he use of human MAb or humanized MAb to key epitopes of infectious pathogens may further define the humoral response with significant therapeutic potential."[26] Accordingly, this review provides ample evidence of the use of antibodies to both prevent and treat infectious diseases, including staphylococcal infections, and validates future therapies, including monoclonal antibodies as having great potential.

***Acknowledgement of Withdrawal of Previous Rejections***

Applicants gratefully acknowledge the withdrawal of the following previous rejections:

The Examiner has withdrawn the rejection of claim 67 under 37 CFR 1.75(c) as being of improper dependent form in light of cancellation of the claim.

The Examiner has withdrawn the rejection of claims 77, 81, 86-87, 93 and 104-115 under the judicially created doctrine of obviousness-type double patenting, as being unpatentable over claims 53-58, 79-83, 91-92, and 96 of copending U.S. Application No. 11/193,440 in light of issuance as US 7,511,122.

***Rejection of Claims 61, 77, 79-81, 86-87, 93, 95, 101 and 104-115***

***Under Doctrine of Obviousness-type Double Patenting***

The Examiner has maintained the rejection of claims 61, 77, 79, 93 and 95 under the judicially created doctrine of obviousness-type double patenting, as being unpatentable over claims 1-7, 9-12 and 14-19 of U.S. Patent No. 6,610,293. The Examiner has also maintained the rejection of claims 61, 101 and 104-115 under the judicially created doctrine of obviousness-type

[23] Keller and Stiehm at page 605, left column, second paragraph under the subheading "Infection in High-Risk Infants".
[24] Keller and Stiehm at page 605, left column, third paragraph under the subheading "Infection in High-Risk Infants".
[25] Keller and Stiehm at page 605, left column, last paragraph under the subheading "Infection in High-Risk Infants".
[26] Keller and Stiehm at page 610, left column, first paragraph under the subheading "LOOK TO THE FUTURE".

double patenting, as being unpatentable over claims 1-6, 9-12 and 14-19 of U.S. Patent No. 6,610,293. Applicants have filed on even date herewith a terminal disclaimer disclaiming the terminal part of any patent granted on the above-identified application that would extend beyond the expiration date of U.S. Patent No. 6,610,293.

The Examiner has also maintained the provisional rejection of claims 77, 79-81, 86-87 and 93 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 40-43, 47-68 and 72 of copending Application No. 10/323,926. This is a *provisional* obviousness-type double patenting rejection because the conflicting claims have not in fact been patented. If appropriate, Applicants will address any obviousness-type double patenting issues upon an indication of allowance of claims in Application No. 10/323,926 or in the instant application.

The Examiner has issued a new grounds of rejection of claims 77, 79-81, 86-87, 93, 101 and 104-115 under the judicially created doctrine of obviousness-type double patenting, as being unpatentable over claims 1, 20-21, 23, 27, 47, 49, 51-54, 56, 76 and 78 of U.S. Patent No. 7,511,122. Applicants have filed on even date herewith a terminal disclaimer disclaiming the terminal part of any patent granted on the above-identified application that would extend beyond the expiration date of U.S. Patent No. 7,511,122.

***Rejection of Claims 61-63, 65-66, 79-81, 86-87, 91, 94, 101 and 114-115 Under Section 112, First Paragraph***

The Examiner has maintained the rejection claims 61-63, 65-66, 79-81, 86-87, 91, 94, 101 and 114-115 under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement.

In maintaining this rejection the Examiner asserts:

> To adequately describe the genus of a composition comprising a monoclonal antibody with the recited characteristics, ***applicant must adequately describe the antigenic determinants (immunoepitopes)*** based on the ability to a) prevent any and all staphylococcal infections in neonates, b) bind to poly-glycerol phosphate of LTA, and c) enhance opsonization of *Staphylococcus epidermidis*, coagulase negative staphylococci, *Staphylococcus aureus*, and *Streptococcus mutans* (emphasis added). (Paper No. 20100207 at page 7, 1st paragraph).

Applicants respectfully traverse the foregoing rejection. The claims are in compliance with the written description requirement of 35 U.S.C. §112, first paragraph as the specification

clearly conveys possession of the claimed invention to one of skill in the art. As the presently claimed invention relates to ***monoclonal antibodies which specifically bind to a fully characterized antigen***, *i.e.,* poly-glycerol phosphate of LTA of Gram positive bacteria, and ***not "antigenic determinants (immunoepitopes)"*** as stated by the Examiner, the written description requirement is met. Additionally, Applicants have demonstrated the therapeutic efficacy of the claimed monoclonal antibodies by showing an increase in neonatal survival following staphylococcal infection. Specifically, Applicants showed that passive immunization of the claimed monoclonal antibodies resulted in protection against infection (*i.e.,* increased survival in a lethal animal model) following staphylococcal infection (see Examples 3, 12 and 13 of the specification).

As amended, claim 61 (and claims which depend there from) are directed to a composition comprising an amount of ***an isolated monoclonal antibody*** effective to ***prevent or treat*** staphylococcal infection in neonates and a pharmaceutically acceptable carrier, wherein the antibody ***specifically binds to poly-glycerol phosphate of Lipoteichoic acid*** (LTA) of *Staphylococcus* and is of the IgG isotype. The claimed antibodies also bind to and enhance opsonization of multiple serotypes of *Staphylococcus epidermidis,* coagulase negative staphylococci, *Staphylococcus aureus* and *Streptococcus mutans* by phagocytic cells with or without complement as compared to an appropriate control in an *in vitro* opsonization assay.

To comply with the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventors had possession of the claimed invention. *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64 (Fed. Cir. 1991). The present specification provides adequate written description of the claimed genus of monoclonal antibodies directed to a fully characterized antigen, poly-glycerol phosphate of LTA of Gram positive bacteria.

The Examiner has taken the position that because "LTA is derived from a 'unique' strain (i.e. the Hays strain)" and "because said monoclonal antibody is capable of binding to LTA from S. epidermidis (Strain Hay), Applicants have not shown that 96-110 monoclonal antibody or the genus of monoclonal are capable of binding to all LTA ***since LTA is not identical in all gram positive bacteria*** (emphasis added)." (Paper No. 20100207 at page 6 first paragraph). The Examiner therefore concludes that

> Applicant have only contemplated that a composition comprising any monoclonal antibody possesses all the recited characteristics of the claim monoclonal antibodies. Consequently, the number of species disclosed by the specification is not representative of a monoclonal antibody of IgG isotype and is not deemed to be representative of the genus encompassed by the instant claims (Paper No. 20100207 at page 6, 1st paragraph).

Thus, the Examiner is taking the position that because LTA is not identical in all gram positive bacteria, Applicants' claimed monoclonal antibodies are not supported by an adequate written description. Applicants' respectfully traverse. All that is required to for adequate written description of an antibody is the disclosure of a fully characterized antigen. LTA is a fully characterized antigen as evidenced by Fisher *et al.*[27] (previously cited by Applicants). Fisher *et al.* analyzed the structure of polyglycerophosphate lipoteichoic acids from 24 Gram positive bacteria of the genera *Bacillus, Enterococcus, Lactobacillus, Lactococcus, Listeria* and *Staphylococcus*. They concluded that

> So it could be demonstrated that poly(glycerophosphate) lipoteichoic acids extracted from a wide range of Gram-positive bacteria have a uniform structure. Each glycolipid moiety uniformly carried a single unbranched poly(glycerophosphate) chain as was deduced from the almost identical molar ratios of glycolipid to phosphorus and phosphomonoester to phosphorus.[28]

Thus, the art has established that LTA is a well characterized antigen, of uniform structure on diverse Gram positive bacteria. However, in the interest in expediting prosecution, Applicants have amended claim 61 to specify that the claimed antibodies specifically bind LTA of *Staphylococcus.* Because the present claims are directed to antibodies that bind a fully characterized antigen, the written description requirement has been met.

Moreover, Federal Circuit decisions, the USTPO Written Description Guidelines and Board of Appeals support Applicants' position. As previously stated, the appropriate legal inquiry is whether "applicants has disclosed a 'fully characterized antigen,' either by its structure, formula, chemical name, or physical properties, or by depositing the protein in a public depository, the applicant can then claim an antibody by its binding affinity to that described

[27] Fisher *et al. Biochem. Cell Biol.* vol. 68, 1990, submitted as Appendix A with Applicant's Amendment and Response filed July 17, 2009.
[28] Fisher *et al.* at page 41, left column, first paragraph.

antigen."[29] The court, when considering an antibody defined by function rather than structure, has looked to the USPTO Written Description Guidelines as persuasive authority, stating that "a claim directed to 'any antibody which is capable of binding to antigen X' would have sufficient support in a written description that disclosed 'fully characterized antigens.'"[30] Example 14 of the revised Written Description Training Materials (Revision 1, March 23, 2008), clearly states that "an adequate description of a purified antigen would have put an inventor in possession of antibodies which bind to the purified antigen." The Board of Patent Appeals and Interferences has followed this precedent and found a claim to monoclonal antibody that "binds an epitope within amino acids 412-562 of the progesterone receptor B form" to be supported by an adequate written description.[31] The Board reasoned as follows:

> The Examiner appears to be requiring that the Specification disclose both the specific epitope recognized by the antibody (*see, e.g.*, FF10), as well as the structure of the antibody (*see, e.g.*, FF9). ***All that is required, however, for adequate written description of an antibody is the disclosure of a fully characterized antigen***, which requirement is met by the Specification (FF5). ***We decline to read into that requirement that the Specification also disclose the specific epitope bound by the antibody, or the structure of the antibody.*** (***emphasis added***)

The presently claimed monoclonal antibodies ***specifically bind poly-glycerol phosphate of LTA of Staphylococcus***. Poly-glycerol phosphate is a fully characterized antigen. Its chemical structure is described in the present specification and was well known in the art at the time of filing. Moreover, because the LTA backbone is composed of repeating units of poly-glycerol phosphate, it represents a small number of defined and well characterized epitopes.

As a polymeric structure, the poly-glycerol phosphate of LTA has the characteristics of a hapten, a simple antigenic determinant with well defined antigen binding. In order to study antibody specificity researchers have often studied antibodies raised against haptens.[32] While haptens can bind antibodies, they are unable to elicit an antibody response *in vivo* because of their inability to directly stimulate T or B cells. These haptens can be conjugated to larger carrier

[29] *Noelle v. Lederman*, 355 F.3d 1343, 1349 (Fed. Cir. 2004).
[30] *Id.*
[31] *Ex parte* Hiaying Xia and Zhida Huang. Appeal 2008-3329 (Application 10/242,092). Decided January 28, 2009.
[32] G. N. Trump and S. J. Singer *PNAS* 66(2):411-418 (1970) (submitted as document C18 on the 1449 filed on July 17, 2009).

molecules which can engage T cells and thereby induce an antibody response against the hapten. Because haptens are single determinants as compared to most antigens which are comprised of multiple determinants the antibodies that haptens induce are very restricted and homogeneous in nature. One of the most well studied haptens is those of carbohydrate antigens. While the size of a carbohydrate antigen may be quite large, it is made of multiple repeating units of a single oligosaccharide unit, usually 1-5 sugars in length. Researchers have found that the antibody response to these haptens is determined by the oligosaccharide unit rather than by its conformation.[33] Because LTA is a linear polymer of repeating units of poly-glycerol phosphate it represents a simple antigenic determinant of known structure. As the present claims are directed to antibodies that bind a fully characterized antigen, namely poly-glycerol phosphate of LTA of Gram positive bacteria, the written description requirement has been met.

Despite this legal precedent, the Examiner, however, has maintained this rejection on the grounds that "absent a detailed and particular description of a representative number, or at least a substantial number of the members of the ***genus of immunoepitopes***, the skilled artisan could not immediately recognize or distinguish members of the claimed genus of a composition comprising a monoclonal antibody with the recited activities (emphasis added)." The Examiner's reasoning is set forth in the following quotes:

> To adequately describe the genus of a composition comprising a monoclonal antibody with the recited characteristics, applicant must adequately describe ***the antigenic determinants (immunoepitopes)*** based on the ability to a) prevent any and all staphylococcal infections in neonates, b) bind to poly-glycerol phosphate of LTA, and c) enhance opsonization of *Staphylococcus epidermidis*, coagulase negative staphylococci, *Staphylococcus aureus*, and *Streptococcus mutans* (emphasis added)." (Paper No. 20100207 at page 7, 1st paragraph).

> The specification, does not disclose distinguishing and identifying features of a representative number of members of the genus of a composition comprising a monoclonal antibody of the IgG isotype, to which the claims are drawn, such as a correlation between the ***structure of the immunoepitope*** and its recited function (emphasis added)." (Paper No. 20100207 at page 8, 2nd paragraph).

> Moreover a ***vaccine*** is defined as "a prophylactic or therapeutic material containing ***antigens derived from one or more pathogenic organisms*** which, on administration to

[33] V.L. Hegde and Y.P. Venkatesh *Immunobiology* 212 (2007) 119-128 (submitted as document C8 on the 1449 filed on July 17, 2009).

man or animal, will stimulate active immunity and protect against infection with these or related organism (i.e. produce protective immunity) (emphasis added)." (Paper No. 20100207 at page 9, 1st paragraph)

The *Guidelines* further state, "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species *cannot* be achieved by disclosing only one species within the genus" (Id. at 1106); accordingly, it follows that an adequate written description of a genus cannot be achieved in the absence of a disclosure of at least one species within the genus. As evidenced by Greenspan et al. (*Nature Biotechnology* 7:936-937, 1999), ***defining epitopes*** is not as easy as it seems (emphasis added)." (Paper No. 20100207 at page 10, 2nd paragraph).

Therefore, absent a detailed and particular description of a representative number, or at least a substantial number of the members of the ***genus of immunoepitopes***, the skilled artisan could not immediately recognize or distinguish members of the claimed genus of a composition comprising a monoclonal antibody with the recited activities. Therefore, because the art is unpredictable, in accordance with the *Guidelines*, ***the description of immunoepitopes (antigenic determinants)*** is not deemed representative of the genus of a composition comprising a monoclonal antibody to which the claims refer and therefore the claimed invention is not properly disclosed." (Paper No. 20100207 at page 10, 2nd paragraph).

Thus, the Examiner appears to base her rejection on the lack of description in Applicants' specification of "immunoepitopes" or "antigenic determinants" and cites Greenspan *et al.* (Nature Biotech. 7:936-937, 1999) in support of her position that defining epitopes is unpredictable. However, Applicants' invention is not a vaccine in which an epitope from a protein antigen is used to induce an immune response in a subject, but rather is directed to monoclonal antibodies which specifically bind poly-glycerol phosphate of LTA. As the claimed invention is directed to monoclonal antibodies, the proper legal inquiry is whether Applicants' specification discloses a fully characterized antigen, LTA of Gram positive bacteria, and, if so, the written description requirement is satisfied.

Moreover, even with respect to claims directed to monoclonal antibodies, it is legally improper for the Examiner to require that Applicants' disclose a particular epitope to which the antibody binds. As stated by the Board in *Ex Parte Xia*, the specific epitope recognized by the antibody need not be disclosed. This is despite the fact that there is significant epitope variability in an amino acid protein of 151 amino acid residues recited in the claims before the Board in *Ex Parte Xia*. In contrast, the LTA backbone is composed of repeating units of poly-glycerol phosphate, thus representing a small number of defined and well characterized epitopes.

Because the present claims are directed to antibodies that bind a fully characterized antigen, the written description requirement has been met.

Furthermore, with respect to generic claims, the Court has held that it is not necessary that every permutation within a generally operable invention be effective for an applicant to obtain a generic claim, provided that the effect is sufficiently demonstrated to characterize a generic invention. *Capon v. Eshhar*, 418 F.3d 1349, 1359 (Fed. Cir. 2005). Likewise, it is well established that for claims directed to genetic material, "a statement such as 'vertebrate insulin cDNA' or 'mammalian insulin cDNA,' without more is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function." *Regents of the University of California v. Eli Lilly and Co.,* 119 F. 3d, 1559, 1568, 43 USPQ2d 1398 (Fed. Cir. 1997). Applicants note that the facts in *Eli Lilly* are not analogous with to the present application. The claims of the present application, however, recite more than a mere function. In particular, claim 61 provides a recitation of structural features common to members of the genus of monoclonal antibodies in that the members of the genus have the common structural feature of being specifically binding a fully characterized antigen, poly-glycerol phosphate of LTA of *Staphylococcus* and are of the IgG isotype. In addition, the specification teaches that there is a correlation between the structure of a monoclonal antibody which specifically binds poly-glycerol phosphate of LTA and the function of binding to and enhancing opsonization of *Staphylococcus epidermidis,* coagulase negative staphylococci, *Staphylococcus aureus* and *Streptococcus mutans* (*see e.g.,* Examples 2, 3 and 7). Moreover, Applicants have described at least 3 antibodies of the claimed genus.

In particular, Example 1 of the present specification describes the preparation of monoclonal antibodies (and hybridomas) made using an antigen preparation from heat killed *S. epidermidis*. Examples 2 and 3 further show that the resultant antibodies are opsonic, and that they confer *in vivo* protective effects against *staphylococci*. Example 7 of the specification further shows binding of an antibody within the scope of the present claims (Ab 96-110, also referred to as "A110") to LTA from *S. mutans*, *S. aureus* and *S. faecalis* (Tables 8 and 9 of the specification) and that it enhances the opsonization for both coagulase positive and coagulase negative staphylococci (see page 53, paragraph 2 of the specification). A chimeric version of this antibody was also created and shown to be opsonic and provide protective efficacy *in vivo* (see Examples 11-13 of the specification).

This disclosure provides a person of ordinary skill in the art with structural information for every member of the genus (*i.e.,* the ability to specifically bind a fully characterized antigen, poly-glycerol phosphate of LTA) that falls within the scope of the claim as well as a correlation with the functional characteristics possessed by members of the genus and recited in the claims. In view of this disclosure, one skilled in the art would reasonably conclude that the inventors had possession of a composition of monoclonal antibodies which specifically bind LTA of *Staphylococcus* and enhance opsonization of multiple serotypes of *Staphylococcus epidermidis,* coagulase negative staphylococci, *Staphylococcus aureus* and *Streptococcus mutans.*

That Applicants provide a disclosure sufficient to demonstrate possession of the claimed genus of monoclonal antibodies is further demonstrated by the identification and characterization of additional anti-LTA antibodies within the scope of the present claims (*see, e.g.,* U.S. Pub. No. 2004/0052779). Two monoclonal antibodies, A120 and 391.4, having a high degree of sequence similarity to the A110 antibody (which corresponds to the same CDR regions as Ab 96-110 of the present application[34]), were identified by Applicants and shown to specifically bind LTA and bind to and enhance opsonization of Gram positive and negative bacteria.[35] In fact, the Applicants observed "the level of homology between the M110, M120, and MAb-391.4 variable regions may indicate that opsonic antibodies to LTA recognize a nearly identical epitope using nearly identical modes of binding, and that this mode of binding is important to their functional activity."[36]

In view of the above, the present specification describes the claimed invention in sufficient detail that one of ordinary skill in the art can reasonably conclude that the inventors were in possession of the claimed invention at the time of filing. Applicants, therefore, request reconsideration and withdrawal of this rejection.

***Rejection of Claims 77, 79-81, 86-87, 91, 93-95, and 104-113 Under Section 112, First Paragraph***

[34] Antibodies A110 and 96-110 differ only in the terminal amino acids of the light chain (*i.e.,* one amino acid difference on each of the N and C terminal positions).
[35] See Examples 1, 2, 5, 6, and 8 of the '779 Publication and Examples 2, 7, and 11 of the present Application.
[36] See paragraph [0196] of the '779 Publication.

The Examiner has maintained the rejection of claims 77, 79-81,86-87,91, 93-95, and 104-113 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. In particular, the Examiner has stated that "Applicant has not demonstrated that a composition comprising variants of monoclonal antibody of IgG isotype aforementioned above is capable binding to polyglycerol phosphate of LTA of all gram positive bacteria species." (Paper No. 20100207 at page 12, first paragraph). The Examiner has also stated

> Moreover, the specification fails to disclose which amino acid residues are essential to the function of the immunoepitope or which amino acids might be replaced so that the resultant immunoepitope retains the activity of its parent, or by which other amino acids the essential amino acids might be replaced so that the resultant immunoepitope retains the activity of its parent. Also the specification fails to disclose which variable regions of the heavy and light chain of a monoclonal antibody of SEQ ID NO: 87 and 89; and of the monoclonal antibody 96-110 that are essential to the function of the immunoepitope and are able to retains its the activity.[37]

Applicants respectfully traverse this rejection. As noted above, and contrary to the Examiner's suggestion, claims directed to a genus of monoclonal antibodies are adequately described based on the disclosure of a fully characterized antigen. Polyglycerol phosphate of LTA is a fully characterized antigen. Accordingly, claims 77, 79-81,86-87,91, 93-95, and 104-113 meet the written description requirement. Furthermore, the rejected claims are supported by a structure function correlation which requires the claimed antibodies, or antigen binding fragments thereof, to specifically bind to poly-glycerol phosphate of LTA of Gram positive bacteria.

Moreover, Applicants note that claims 77, 93, 95, 104, and 105 are directed to specific antibodies comprising the antigen binding regions (CDRs) set forth in SEQ ID NO: 87 or SEQ ID NO:89 (claim 77), antibodies having the specific heavy or light chain variable regions set forth in SEQ ID NO:s 87 and 89 (claims 104 and 105), or antibodies having 70% identity or more to the heavy or light chain variable genes set forth in SEQ ID NO: 87 or 89. Claims dependent upon claim 77 further require that the claimed antibodies, or antigen binding fragments thereof, specifically bind to poly-glycerol phosphate of LTA of Gram positive bacteria.

[37] Pages 11-12 of the instant Office Action.

Example 5 of the Written Description Training Materials specifically outlines a situation where a genus of claimed proteins are defined by their function (*i.e.*, ability to bind a second protein) and a partial protein sequence (*i.e.*, SEQ ID NO:1 having only 10 amino acids). In such a fact pattern, the Training Materials note that a claim meets the written description requirement. Likewise, the recitation of a particular amino acid sequence (*e.g.*, SEQ ID NO: 87 or SEQ ID NO:89) coupled to the specific functional requirement of binding to a poly-glycerol phosphate provides a correlation between structure and function of the antibodies and therefore meets the written description requirement.[38]

In summary, because the claimed antibodies, or antigen binding fragments thereof are directed to a fully characterized antigen, and, alternatively, because the claimed antibodies are described to have a clear correlation between their structure and function, Applicants request the rejection of claims 77, 79-81,86-87,91, 93-95, and 104-113 under 35 U.S.C. § 112, first paragraph be withdrawn.

***Rejection of Claims 61-63, 65-68, 79-81, 86-87, 91, 94, 101, and 114-115 Under Section 112, First Paragraph***

The Examiner has maintained the rejection of claims 61-63, 65-68, 79-81, 86-87, 91, 94, 101, and 114-115 under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. In particular, the Examiner has alleged that the "specification is not enabled for a composition comprising an amount of an isolated a monoclonal antibody effective to prevent staphylococcal infection in neonates and a pharmaceutically acceptable carrier." The Examiner has further alleged that the specification does not enable a person skilled in the art to make and use the claimed invention.

Applicants traverse the foregoing rejection on the grounds that the amount of direction and guidance disclosed in the specification is sufficient to enable the skilled artisan to make and use the claimed invention.

[38] Also see In re Alonso, 2008 U.S. App. LEXIS 24320, 16-17 (Fed. Cir. Oct. 30, 2008) stating: "...we have found adequate written descriptive support for a claimed invention where the disclosure specifies ..... functional characteristics when coupled with a known or disclosed correlation between function and structure...' Enzo, 323 F.3d at 964"

The Examiner acknowledged that the specification discloses an antibody that promotes clearance of staphylococci from the blood and promotes survival of mice upon treatment with an antibody of the invention. However, the Examiner insisted that the specification is limited to survival of neonates and cannot be drawn to *prevention* of staphylococcus infection. This is based upon the Examiner's construction of the term "prevention" to be equivalent to administration of a vaccine. Applicants note that the present claims are not directed to a vaccine or an active immunization in which an antigen or fragment thereof is administered to a host to induce a protective immune response to antigen. Instead, the present invention is directed to a composition comprising anti-LTA monoclonal antibodies which have been shown to opsonize multiple Gram positive bacteria and to protect against infection when administered *in vivo*. Thus, there is no need for the host to generate a protective antibody response to invading bacteria, as the monoclonal antibody compositions of the invention provide protection against staphylococcal infection. The specification describes protective administration of a composition of the present invention on page 23:

> A further embodiment of the present invention is a method of preventing such infections, comprising administering a prophylactically effective amount of a pharmaceutical composition comprising the anti-LTA antibody (whether polyclonal or monoclonal or chimeric, including fragments, regions, and derivatives thereof) and a pharmaceutically acceptable carrier.
>
> A prophylactically effective amount is an amount reasonably believed to provide some measure of prevention of infection by Gram positive bacteria.

Accordingly, prevention, as described in Applicants' specification, is not equivalent to vaccination, but involves treatment or prophylactic treatment of a subject.

Furthermore, the present specification fully enables one of skill in the art to make and use the claimed invention because the specification discloses methods to make and test antibodies of the invention, and because the specification demonstrates their use. According to the MPEP:

> "As long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. 112 is satisfied." MPEP 2164.01(b)
>
> and
>
> "If a statement of utility in the specification contains within it a connotation of how to use, and/or the art recognizes that standard modes of

administration are known and contemplated, 35 U.S.C. 112 is satisfied." MPEP 2164.01(c)

As described above, the specification describes prophylactic treatment using antibodies of the invention. Assays to determine clearance of bacteria and protection are described in the specification at least on page 32, paragraph 2 through page 33. Example 2 describes the ability of an antibody of the invention to opsonise bacteria and states that "[s]uch an antibody would be capable of promoting clearance of Staphylococci that have invaded a host and would be useful therapeutic agent." Furthermore, Example 3 (entitled "In Vivo Protective Efficacy) demonstrates that administration of an antibody of the invention before and after infection confers enhanced survival, thereby demonstrating that the antibody confers a protective effect.

The Examiner provides a discussion of several of the Wands factors (MPEP 2164.01(A)), and we address the Examiner's points individually as follows.

**Nature of the Invention**

The Examiner asserts that the claims as drawn to any composition comprising an isolated monoclonal antibody of IgG isotype effective prevent staphylococcal infection in neonates. In contrast to the Examiner's characterization, the present claims are directed specifically to anti-LTA antibodies, not ***any*** antibody isotype effective to prophylactically or therapeutically treat staphylococcal infection in neonates.

**Breadth of the claims**

As the Examiner describes, the claims as amended encompass any composition comprising an isolated monoclonal antibody effective to prevent or treat staphylococcal infection in neonates and a pharmaceutically acceptable carrier, wherein the antibody specifically binds to poly-glycerol phosphate of Lipoteichoic acid (LTA) of *Staphylococcus* and is of the IgG isotype, wherein the antibody binds to and enhances opsonization of multiple serotypes of *Staphylococcus epidermidis,* coagulase negative staphylococci, *Staphylococcus aureus* and *Streptococcus mutans* by phagocytic cells. However, techniques for making antibodies are routine in the art, and require no undue

experimentation. Moreover, the specification provides ample guidance for producing the presently claimed antibodies. In particular, Example 1 describes preparation of an antigen and production of candidate immunoglobulin molecules. Examples 2 and 3 describe methods to test the opsonic effect of antibodies, and demonstrate that administration of an antibody of the invention before and after infection confers enhanced survival, thereby demonstrating that the antibody confers a protective effect. Example 7 of the specification describes methods to test whether an exemplary antibody of the invention binds the LTA of staphylococci. Examples 11-13 further describe methods to humanize antibodies of the invention.

Moreover, the level of one of ordinary skill is high. A skilled artisan would clearly understand, given the state of the art at the time of filing and the disclosure of the present specification, how to make and use antibodies of the present invention.

**Guidance of the Specification/ Existence of Working Examples**

As described above, the guidance provided by the Specification is extensive. The Specification provides 13 Examples describing antigen preparation, antibody and hybridoma creation (Example 1), tests for opsonic activity (Examples 2 and 11), description and testing of in vivo protection (Examples 3 and 12), binding and antigen characterization (Examples 4-7), humanization (Example 8), and chimeric antibody production (Examples 9 and 10).

The Examiner insists that "[t]he claimed invention is drawn to prevention of staphylococcal infection and as a result prevention is correlated to a vaccine. A vaccine by definition must provide protection against an infection demonstrable by challenge experiments." However, as explained above, the present invention is not directed to active immunization, but rather to the administration of protective antibodies to the host.

The Examiner asserts that the data "merely" shows that the composition increases the number of neonates that survive a Staphylococcal infection and thus fails to show prevention or protection against Staphylococcus species. Applicants submit that the evidence of increased survival shown in Examples 3 and 12 is affirmative evidence of

protection and therefore prevention of Staphylococcal infection. The claimed antibodies are clearly shown to be successful in treating and protecting animals from Staphylococcal infection.

**State of the Art**

The Examiner discusses active immunization in general and cites several sources in the "vaccine art" that describe the ability of an antigen to stimulate an immune response in a host. The Examiner's discussion and the cited references are not relevant because the present invention is not drawn to methods of active immunization, but, as described above, to administration of a composition of anti-LTA antibodies to neonates to prophylactically or therapeutically treat Staphylococcal infection.

The use of antibodies as a prophylactic agent to prevent or reduce the effects of an infection is well established in the art.[39] Indeed, antibody compositions have been successfully used to treat or prevent infection by a wide variety of pathogenic agents including viruses, bacteria, and toxins. For example, Volk *et al.*[40] showed that administration of monoclonal antibodies is effective to neutralize tetanus toxin. In their studies, toxin was mixed with monoclonal antibodies and, after a short incubation, injected into mice. Mice still surviving on day 4 (where control mice died on days 2 or 3) were considered protected from the toxin. Indeed, antibody compositions directed to tetanus toxin are currently being used in the clinic to protect patients who are potentially exposed to tetanus. HyperTet™ S/D is one example of an immunogloblulin composition which may be administered to patients to neutralize tetanus toxin.[41]

Likewise, monoclonal antibodies have been used to prevent viral and bacterial infection. For example, Meuleman *et al.*[42] showed that prophylactic administration of anti-CD81 antibodies was effective at preventing Hepatitis C virus infection in animals[43].

---

[39] See also Applicants' previous discussion herein under the subheading "Prevention and Treatment of Infection" and Keller and Stiehm (Appendix G).
[40] *Infection and Immunity*. 1984. 45(3):604-609. Submitted with Applicants Amendment and Response filed July 17, 2009.
[41] See the information provided online by Talecris Biotherapeutics: http://www.talecris-pi.info/inserts/hypertet.pdf .
[42] *Hepatology*. 2008. 48(6):1761-1768. Submitted as Appendix B with Applicants Amendment and Response filed July 17, 2009.
[43] Meuleman *et al.* at page 1764, column 1

Similarly, Rosok *et al.*[44] found that administration of monoclonal antibodies against the flagellum of *Pseudomonas aeruginosa* "provided specific and significant prophylactic and therapeutic protection."[45] Rosok *et al.* found that all animals which received antibody injections prior to bacterial infection survived, as compared to about 20% survival in control animals.[46] Rosok *et al.* also showed that the monoclonal antibodies were effective for treating animals after infection, where 70%-90% of treated post-infection animals were protected.[47]

Similar to the composition of Rosok *et al.*, the presently claimed invention is directed to a composition of monoclonal antibodies against pathogenic bacteria. As described in Applicants' specification, administration of a composition of anti-LTA antibodies protected animals from infection. Specifically, in Example 3 of the present specification Applicants showed that administration of an antibody composition of the invention prior to and after bacterial infection enhanced survival in a rat neonate model. Example 12 of the specification further shows protective efficacy of a chimeric antibody of the invention for Adult CF1 mice against bacterial infection, while Example 13 shows efficacy of the chimeric antibody in a neonatal rat model. Accordingly, Applicants specification demonstrates the efficacy of administering a composition of anti-LTA antibodies to treat or prevent Staphylococcal infection.

Finally, there are FDA approved antibody compositions currently in use in humans to treat and prevent pathogenic infection. For example, the drug Synagis® (Palivizumab) is a protective antibody against respiratory syncytial virus (RSV). The manufacturer, MedImmune, describes Synagis® as follows: "Even though Synagis is given as a shot by your healthcare provider, ***it's not a vaccine and it works differently. Each Synagis shot provides a dose of virus-fighting substances called antibodies that help prevent RSV from infecting your baby's lungs***"(***emphasis added***).[48] Thus, like the presently claimed composition, Synagis® is administered to high-risk infants ***prior to RSV***

[44] *Infection and Immunity*. 1990. 3891-3821. Submitted as Appendix C with Applicants Amendment and Response filed July 17, 2009.
[45] See Rosok *et al.* Abstract, page 3819
[46] Rosok *et al.* at page 3824, column 2.
[47] Rosok *et al.*, at page 3825, column 1.
[48] Taken from "http://www.synagis.com/how-synagis-works.aspx" on July 8, 2009.

***infection to prevent disease***, although regular administration may be continued after infection.

Moreover, since the time of filing, antibodies of the present invention have been tested in clinical trials and found to be safe in both adults and neonates. One particular antibody, Pagibaximab®, has been shown to be effective against >90% of coagulase negative staphylococci strains, and demonstrate >90% bacterial killing at <10μg/ml.[49]

In summary, a skilled artisan would understand, given the disclosure of the specification, how to make and use the presently claimed invention. Furthermore, the amount of guidance provided by the specification (as evidenced above) and the successful application of art-recognized antibodies for prophylaxis and treatment of disease would have led the skilled artisan to expect that the present invention would be useful as claimed with no undue experimentation. Applicants respectfully request reconsideration and withdrawal of the rejection of claims 61-63, 65-68, 79-81, 86-87, 91, 94, 101, and 114-115 under 35 U.S.C. § 112, first paragraph.

[49] See page S32, column 2 of Weisman. Archives de pediatrie 14 (2007) S31-S34, submitted as Appendix D with Applicants Amendment and Response filed July 17, 2009.

## CONCLUSION

In view of the above amendment, Applicants believe the pending application is in condition for allowance. If a telephone conversation with Applicants' attorney would expedite the prosecution of the above-identified application, the Examiner is urged to call the undersigned at (617) 227-7400. If there are any fees due, please charge our Deposit Account No. 12-0080, under Order No. SYNI-003CN from which the undersigned is authorized to draw.

Dated: June 10, 2010

Respectfully submitted,

Electronic Signature: /Amy E. Mandragouras/
Amy E. Mandragouras, Esq.
Registration No.: 36,207
LAHIVE & COCKFIELD, LLP
One Post Office Square
Boston, Massachusetts 02109-2127
(617) 227-7400
(617) 742-4214 (Fax)
Attorney/Agent For Applicants